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(54) Title: TREATMENT OF OPIATE WITHDRAWAL SYNDROME

(57) Abstract

Opiate withdrawal syndrome is treated by administration of a D2 receptor agonist, preferably a selective D2 receptor agonist. Representative compounds include apomorphine, N-allylnoraporphine, pergolide, quinpirole, propylnorapomorphine, bromocryptine, trihydroxyaporphine, methylenedioxy-propylnoraporphine, terguride and hydroxyphenyl-N-propylpiperidine.

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TREATMENT OF OPIATE WITHDRAWAL SYNDROME

Field of the Invention

The invention relates to the treatment of opiate withdrawal syndrome, particularly treatment of withdrawal syndrome with compounds which are agonists of the D2 dopaminergic receptor in the brain.

Reference to Government Grant

The invention described herein was supported in part by the National Institutes of Health, pursuant to grants DA06214 and DA05387. The United States government has certain rights in the invention.

Background of the Invention

Withdrawal from opiate dependency is characterized by a combination of behavioral and physical manifestations generally divided into purposive and nonpurposive behaviors. Purposive behavior, which is goal oriented, is directed to obtaining more drug. Nonpurposive behavior is not goal oriented.

Nonpurposive symptoms, which include lacrimation, rhinorrhea, yawning and sweating, appear 8-12 hours after the last dose. Additional withdrawal symptoms which then ensue include dilated pupils, anorexia, gooseflesh, restlessness, irritability, and tremor. Nonpurposive symptoms of heroin and morphine addiction peak at 48-72 hours. As the withdrawal syndrome approaches peak intensity, the patient exhibits increasing irritability, insomnia, marked anorexia, violent yawning, severe sneezing, lacrimation and coryza. Weakness and depression are pronounced. Nausea and vomiting are common, as are intestinal spasm and diarrhea. Heart rate and blood pressure are elevated. Marked chilliness, al-

tering with flushing and excessive sweating, is characteristic. Pilomotor activity resulting in waves of gooseflesh is prominent. Abdominal cramps and pains in the bones and muscles of the back and extremities are also characteristic, as are muscle spasms and kicking movements. Other signs of central nervous system hyperexcitability include ejaculation in men and orgasm in women. The respiratory response to carbon dioxide which is decreased during opiate administration is exaggerated during withdrawal. Rebound phenomena are also observed in the endocrine system.

Without treatment, the withdrawal syndrome runs its course and most of the grossly observable symptoms disappear in 7-10 days, but it is not certain how long it takes to completely restore physiological equilibrium.

The opiate withdrawal syndrome is treated primarily by administration of another opiate or by the non-opiate clonidine. However, all of these agents have serious side effects, including hypotension, sedation, respiratory depression and their own withdrawal symptoms that occur after prolonged administration. Oral methadone substitution is the presently the principal treatment for heroin withdrawal. However, methadone is itself an opiate. Additional therapeutic agents free of the deleterious side effects of the present withdrawal-treating agents are needed, both as a treatment for opiate withdrawal and as an adjunct to facilitate abstinence.

Nuclei comprise masses of gray matter of groups of nerve cells in the central nervous system One such nucleus, the nucleus accumbens, forms the floor of the caudal part of the anterior prolongation of the lateral ventricle of the brain. While the nucleus accumbens is prominently implicated in the reinforcing effects of abused drugs (Vaccarino et al., Psychopharmacology 86, 37-41, 1985; Wise, Neurosci. Biobehav. Rev. 13, 129-141, 1989; Dworkin et al., Pharmacol. Biochem. Behav. 29, 175-179, 1088), it is generally though that the accumbens plays only a negligible role in the overt somatic signs of opiate withdrawal (Koob et al., Psychopharmacology 98, 530-535, 1989; Stinus et al., Neuroscience 37, 767-776, 1990; Bozarth and Wise, Science 224, 516-519, 1984).

Summary of the Invention

It is an object of the invention to provide for the treatment of opiate addiction, without the side effects of existing treatment modalities.

It is an object of the invention to provide for the alleviation of the various symptoms associated with opiate withdrawal.

These and other objects will be apparent from the following description.

A method for treating opiate withdraw is provided. A withdrawal symptom-alleviating effective amount of a D2 receptor agonist is administered to a patient in need of such treatment.

Description of the Figures

Fig. 1 is a graph of the degree of indicated symptoms observed during naloxone-precipitated withdrawal in rats protected with various doses of intraperitoneal apomorphine, which is a D2 receptor agonist.

Fig. 2 is a graph of the degree of indicated symptoms observed during naloxone-precipitated withdrawal in rats protected with various doses of intraperitoneal propylnorapomorphine, another D2 receptor agonist.

Fig. 3 is a graph of the degree of indicated symptoms observed during naloxone-precipitated withdrawal in rats protected with various doses of intra-accumbally administered propylnorapomorphine.

Fig. 4 is a graph of the degree of indicated symptoms observed during naloxone-precipitated withdrawal in rats treated with the indicated doses of intra-accumbally administered propylnorapomorphine plus systemic flupenthixol; intra-accumbally administered SKF-38393, which is a D1 receptor agonist; or intra-striatal propylnorapomorphine.

Fig. 5 shows the degree of place aversion syndrome observed during naloxone-precipitated withdrawal of morphine-dependent rats treated with and without systemic propylnorapomorphine.

Detailed Description of the Invention

D1 and D2 receptors are a subclassification of dopamine receptors in the brain based in (i) differential binding of certain ligands to sites that also bind dopamine with high affinity, and (ii) different postsynaptic effects found for dopamine depending on its site of action and on the specific agonist employed. D1 receptors are thought to be widely distributed but not present on dopamine neurons, and cause increased production of the second messenger molecule cAMP inside target cells. D2 receptors are thought to be located on dopamine neurons themselves and serve a feedback inhibition of dopamine activity. D2 receptors are also located on other neurons, and are generally found to decrease cAMP production.

We have surprisingly found that D2 dopaminergic receptor activity in the nucleus accumbens area potently regulates somatic and aversive symptoms of opiate withdrawal. We have found that activation of D2 receptors within the accumbens prevents somatic signs of opiate withdrawal, and that administration of D2 receptor agonists attenuates somatic and aversive withdrawal symptoms.

The D2 receptor agonists employed in the practice of the present invention to treat opiate withdrawal, unlike the presently preferred drug for this purpose, methadone, are not themselves opiates. Hence, D2 receptor agonists do not induce dependence and are lacking in abuse potential. Moreover, the D2 receptor agonists as a class of drugs are not generally known to induce the more serious side effects of prior withdrawal-treating agents.

Opiate withdrawal symptoms are treated according to the present invention by administering to a patient in need of such treatment a withdrawal symptom-alleviating effective amount of a compound which comprises a D2 receptor agonist. By "D2 receptor agonist is meant" any substance which displaces the dopaminergic compounds spiperone or raclopride from brain tissue with a K_i in the range of 1-10 nM. Appropriate radioreceptor assays for determining such K_i values include, for example, Faedda et al., Biochem. Pharmacol. 27: 473-480 (1989), Cohen et al., Neuropharmacolo-

gy 19: 663-668 (1980) and Kula et al., Life Sci. 37: 1051-1057 (1985). Preferably, the D2 receptor agonist is a selective D2 agonist, that is, a compound which preferentially induces activation of the D2 receptor over the D1 receptor. By "selective D2 receptor agonist" is meant a D2 receptor agonist, as defined above, which has a binding affinity for D2 receptors which is at least 100 times greater than the agonist's binding affinity for D1 receptors. The affinity is determined by a conventional dopamine receptor binding assay. A reference which provides exemplification for such an assay is Neumeyer et al., J. Med. Chem. 34, 24-28, 1991.

D2 receptor agonists which are not selective for the D2 receptor, but which are nevertheless capable of attenuating withdrawal symptoms include, for example, apomorphine, N-allylnoraporphine and pergolide. Also, quinpirole is considered a mixed D2/D3 agonist. Selective D2 receptor agonists include, for example, propylnorapomorphine (R-NPA), bromocryptine, trihydroxyaporphine, methylenedioxy-propylnoraporphine (MDO-NPA), terguride, and hydroxyphenyl-N-propylpiperidine. Pharmaceutically acceptable salts of these compounds may be employed.

The compound is administered to an opiate-addicted patient to prevent or alleviate the symptoms associated with opiate withdrawal. Patients are selected for treatment based on the presence of the opiate withdrawal symptoms noted above. The patient is a mammal, more particularly, a human being.

The present invention may be used to counteract withdrawal symptoms arising from any opiate addiction. Representative addictive opiates, the withdrawal symptoms of which may be treated according to the practice of the present invention include, for example, heroin, morphine, codeine, methadone, oxycodone, hydromorphone, oxymorphone, levorphanol, hydrocodone, and fentanyl.

The D2 agonist compound may be administered as an adjunct to withdrawal therapy, either alone or in combination with other medications intended for alleviation of opiate withdrawal symptoms. Such other withdrawal-alleviating medications include, for example, methadone and clonidine.

There are no known dangerous interactions between the other treatment agents for opiate withdrawal and the D2 receptor agonist drugs. Thus, it is contemplated that the D2 agonists could be administered along with these other agents. In particular, it is contemplated that a D2 receptor agonist could be given in conjunction with methadone maintenance treatment to more quickly wean patients from methadone.

The D2 receptor agonist is administered in an amount sufficient to induce at least a partial alleviation of one or more or the prominent symptoms comprising opiate withdrawal symptom. The particular dosage of D2 receptor agonist depends upon such factors as the size, weight, sex, and age of the patient; the nature of the addicting opiate; the duration of the patient's addiction; and the severity of the withdrawal symptoms. Most particularly, the dosage will depend upon the nature of the D2 agonist compound. Generally, the dosage will range from about 0.05 to about 200 mg. It is contemplated that a dosage range which is particularly suited for R-NPA is about 0.05-50 mg, preferably about 0.1-10 mg, most preferably about 0.5-5 mg. Ranges may require adjustment for different compounds.

The preferred route of administration of D2 agonist is oral administration, although other routes of administration such as various forms of parenteral administration may be utilized for selected D2 agonists. The D2 agonists are orally administered in a variety of dosage forms suitable for administration of oral pharmaceutical. Solid dosage forms, such as tablets, capsules or caplets, may be employed.

Therapy comprises daily administration of the recommended dosage one or more times daily through the course of the withdrawal period. The dosage may be attenuated as the withdrawal episode runs its course. The particular treatment regimen depends on the nature of the D2 agonist. One typical treatment, which is particularly useful for administration of R-NPA, comprises administration of the above-recommended dosage orally four times daily for about 2-4 weeks. The treatment may be continued for a longer period as needed, if withdrawal symptoms persist.

Successful therapeutic action of the D2 receptor agonist compound can be assessed as the attenuation of withdrawal symptoms. Also, D2 agonist treatment efficacy can be assessed by the ability to decrease the dosage of other treatments, e.g., methadone, needed to maintain abstinence. Treatment success may be further determined by patient interview.

We have found, through the studies described in more detail below, that D2 receptors in the nucleus accumbens area regulate symptoms associated with opiate withdrawal. Major declines in all somatic symptoms have been observed to occur with both peripheral and intra-accumbal administration of a D2 agonist. Our data also indicate that systemic R-NPA also reduces withdrawal aversion measured by place conditioning. Co-administration of D2 antagonists with agonists were observed to prevent the suppression of somatic withdrawal signs, confirming the selectivity of D2 agonist action. Conversely, D2 antagonists when given alone either systemically or in the accumbens elicited withdrawal responses in morphine-dependent animals. While intra-accumbal injections may have diffused and acted at sites other than the nucleus accumbens, similar injections dorsal to the accumbens (a likely site of diffusion from accumbens injections and equally near or close to the ventricle as accumbens sites) were ineffective.

These results indicate marked receptor selectivity in the nucleus accumbens for dopamine-mediated modulation of opiate withdrawal, which involves D2 but not D1 receptors. Without wishing to be bound by any theory, it is possible that D2 receptor activity offsets biochemical changes in accumbens neurons evoked by chronic opiate treatment, and this normalizing effect could be responsible in part for the decrease in withdrawal behaviors observed with D2 agonist administration.

The following studies demonstrate the effects of dopaminergic drugs on the withdrawal behaviors of opiate-treated rats.

Attenuation of Opiate-Precipitated Withdrawal by Systemic Administration of D2 Receptor Agonist

Fifteen minutes prior to receiving a 0.5 mg/kg ip dose of naloxone, rats were pretreated with either vehicle, apomorphine (0.3-2 mg/kg ip) or R-NPA (50-500 μg/kg; ip, n=6-7 per group). The vehicle solution contained saline with 2% ascorbic acid. Instances of the following behaviors were counted for 30 minutes following naloxone administration: wet dog shakes, teeth chatter, writhing, eye twitching, and diarrhea. In addition, animals were scored for the presence or absence of vocalizing on touch, or ptosis, every 10 minutes. No instances of jumping, rhinorrhea or lacrimation were observed during precipitation of withdrawal with this treatment paradigm. Approximately 60% of the animals were scored by a blinded observer. As there were no significant differences in the scoring between blinded and non-blinded observers, these data were pooled. The results are shown in Figs. 1 (apomorphine) and 2 (R-NPA) as the mean number of counts (±SEM) for each behavior measured during naloxone-precipitated withdrawal. Overall F (6,35) values for apomorphine ranged from 4.58 to 72.30, $p<.002$ to $p<.001$ for individual measures. Doses of 0.3 to 2.0 mg/kg were significantly different at each measure from vehicle at $p<.05$. Overall F (6,35) values for systemic R-NPA ranged from 6.4 to 58.56, $p<.001$ to $p<.0001$. Doses of 50-500 μg/kg were significantly different from vehicle for measures of wet dog shakes, teeth chatter, writhing, eye twitch and vocalization, $p<.01$, and diarrhea at $p<.05$ for doses of 100-500 μg.

Thus, systemic administration of the non-selective DA agonist, apomorphine (300 μg - 2 mg/kg, Fig. 1), or the more selective D2 agonist R-NPA (50-500 g/kg, Fig. 2), significantly attenuated all somatic withdrawal symptoms measured. Pretreatment with these dopamine agonists attenuated withdrawal symptoms at the lowest doses tested, and the attenuation appeared to be dose-dependent. Withdrawal-induced diarrhea was less effectively antagonized than the other symptoms.

Attenuation of Opiate-Precipitated Withdrawal by Intra-accumbal Administration of D2 Receptor Agonist

To test the effect of localized delivery of D2 receptor agonist, the following study was performed using

intra-parenchymal administration. Guide cannulae were implanted bilaterally in morphine-dependent animals 2 mm above the injection site. Cannulae were angled at 12° (dorsolateral to ventromedial) to avoid penetrating the ventricle and to prevent possible diffusion if injected into the ventricle by flow upwards along the cannula. The tips of inner cannulae (30 gauge) inserted through these guide cannulae were placed in either the accumbens (AP: 1.7, ML: 3.0, DV: 7.3) or for controls in the dorsal striatum (AP: 1.7, ML: 2.0, DV: 6.0). With this approach accumbens and dorsal striatal placements were approximately equidistant from the ventricle. Following a 7 day recovery period, animals were placed under light halothane anesthesia for the microinjections (0.8 µl volume given bilaterally, 2 min per side, n=50). The vehicle solution was artificial CSF that contained 2% ascorbic acid. Animals were allowed 20 min for recovery before naloxone (0.5 mg/kg ip) was injected. Scoring for withdrawal was the same as in the systemic administration study above. Each animal received at least two withdrawal episodes under different treatment conditions spaced 4 days apart. The order of treatments was counterbalanced. All data are from rats with injection sites histologically confirmed in the accumbens shell or dorsal striatum as indicated. Thirty-nine animals were included in the intra-accumbal injected groups with group n=4-5. The results are shown in Fig. 3.

Overall F (6,29) values for intra-accumbal R-NPA ranged from 11.25 to 23.09, $p < .0001$ for wet dog shakes, teeth chatter, writhing, eye twitching and vocalization. Intra-accumbal R-NPA reduced withdrawal-induced diarrhea less than other signs, and produced a small degree of ptosis when given alone. All R-NPA doses in Fig. 3 were significantly different from vehicle, $p < .01$ at each of these measures except diarrhea, $p < .05$.

Effect of Dopamine Antagonist on D2 Receptor Agonist-induced Attenuation of Opiate-Precipitated Withdraw (Intra-accumbal Administration)

To test the pharmacologic selectivity of microinfused agonists, the preceding study was repeated except

that an antagonist (systemic flupentixol, 0.5 mg/kg) was injected intraperitoneally immediately before halothane anesthesia and intra-accumbal injection of the agonist R-NPA. Alternatively, animals received intra-accumbal administration of the partial D1 receptor agonist SKF-38393 (2-5 mg/kg), or received intra-striatal R-NPA. The results are shown in Fig. 4.

The systemic dopamine antagonist flupentixol completely blocked the ability of intra-accumbal R-NPA to alleviate withdrawal. The only significant difference from vehicle was an increase in wet dog shakes with intra-accumbal SKF 38393, $p < .02$. Similar results were obtained in reversing the withdrawal attenuating effect of R-NPA upon pretreatment of the rats with the dopamine receptor antagonist haloperidol (0.5 mg/kg, n=1, $p < 0.32$; data not shown). In another study, the full D1 agonist SKF 81297 (1-10 mg/kg) was unable to reduce naloxone-precipitated withdrawal symptoms (n=10, $p > 0.4$; data not shown).

Together, these data indicate that dopamine agonists alleviate opiate withdrawal by activation of D2 receptors within the accumbens region of the brain.

Precipitation of Somatic Withdrawal Symptoms By Blockade of Endogenous Accumbal Dopamine Receptors in Morphine-dependant Animals

In yet another study, we tested whether blockade of endogenous accumbal DA receptors could precipitate somatic withdrawal signs. In morphine-dependent animals, but not in non-dependent subjects, systemic injections of the non-selective DA antagonist, flupentixol, or of the more selective D2 antagonist, eticlopride (0.5 to 2 mg/kg for each) precipitated several withdrawal signs, including wet dog shakes, teeth chatter, writing and eye twitching ($p < .01$, n=30). These withdrawal symptoms were manifested within 10 min of injection of the antagonist. In contrast, when the mixtures of DA agonist and antagonist were administered in the previous experiment no withdrawal symptoms were seen in the 15-20 min preceding naloxone administration. These findings suggest that D2 agonists and antagonists were able to offset each other's actions on withdrawal behaviors. In

addition, intra-accumbal injections of either flupentixol or eticlopride (3 μg for each) precipitated similar somatic withdrawal signs in morphine-dependent animals. The intra-accumbal dose needed to produce withdrawal signs was at least fifty-fold lower than when given systemically. Several somatic withdrawal signs precipitated by intra-accumbal DA antagonists were just as severe as when withdrawal was precipitated by systemic naloxone. Other signs were less severe but were still significantly greater than when a DA antagonist (flupentixol, 3 μg) was injected into the striatum or when vehicle was injected into the accumbens.

Attenuation of Opiated-Precipitated Place Aversion by D2 Receptor Agonist

Aversion is another opiate withdrawal symptom. The ability of D2 receptor agonists to attenuate opiate-induced aversion is demonstrated in the following naloxone-induced place aversion assay involving morphine-dependent animals.

A place conditioning apparatus comprising a 70 x 30 x 45 cm box was divided equally into two compartments. The first compartment had a smooth clear Plexiglas® floor, black spots on the rear wall and an almond scent. The second compartment had a rough opaque Plexiglas® floor, black stripes on the rear wall and a coconut scent. Morphine-dependent rats were treated systemically with the D2 agonist R-NPA (50-300 mg/kg) prior to two consecutive days of place conditioning. All rats were tested in the morning 16-18 hours after the last morphine injection. On the first day each rat was allowed to freely explore both compartments of the box and the amount of time spent on each side was recorded for 20 minutes. On Day 2, rats were injected with either saline or R-NPA (50-300 μg/kg ip, n=6 per group), 15 min prior to an injection of either saline or 0.2 mg/kg naloxone (ip). Immediately following the naloxone or saline injection, rats were confined to one side of the box by means of an opaque Plexiglas® divider for 20 min. On Day 3, rats were given the same pre-treatment as on Day 2 and confined to the opposite compartment following either a saline or naloxone injection for 20 min. Animals that received

naloxone on Day 2 received saline on Day 3, and vice versa. On Day 4, rats were given free access to both compartments and the amount of time spent on each side was recorded for 20 min. This design obviated possible affective valence of R-NPA alone by exposing each rat equally to this agent on each side of the chamber.

The results of the study appear in Fig. 5. Aversion scores were calculated by subtracting the amount of time spent in the naloxone-paired environment post-conditioning from the amount of time spent in the same environment prior to conditioning. The treatments in Fig. 5 are the injections given to each group 15 min prior to conditioning on both days 2 and 3. $F(3, 29) = 92.74$ $p < .0001$. Doses of 100-300 μg/kg were significantly different from vehicle, $p < .01$.

Animals that were given R-NPA prior to receiving naloxone failed to develop a place aversion to the naloxone-paired environment (Fig. 5). The dose that blocked the place aversion (100 μg/kg) was the same dose that significantly reduced the somatic signs of withdrawal. A lower dose (50 μg/kg) that was not effective in reducing somatic withdrawal signs was also not effective in reducing withdrawal aversions (Fig. 5).

All references cited with respect to synthetic, preparative and analytical procedures are incorporated herein by reference.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indication the scope of the invention.

CLAIMS

1. A method for treating opiate withdrawal comprising administering to a patient in need of such treatment a withdrawal symptom-alleviating effective amount of a D2 receptor agonist.

2. A method according to claim 1 for treating heroin, morphine or methadone withdrawal.

3. A method according to claim 1 wherein the D2 receptor agonist comprises a selective D2 receptor agonist.

4. A method according to claim 1 wherein the D2 receptor agonist is selected from the group consisting of apomorphine, N-allylnoraporphine, pergolide, quinpirole, propylnorapomorphine, bromocryptine, trihydroxyaporphine, methylenedioxy-propylnoraporphine, terguride and hydroxyphenyl-N-propylpiperidine.

5. A method according to claim 4 wherein the D2 receptor agonist is propylnorapomorphine.

6. A method according to claim 1 comprising oral administration of the D2 receptor agonist.

7. A method according to claim 6 wherein the single dosage amount of agonist administered is from about 0.05 to about 200 mg.

8. A method for alleviating the symptoms of opiate withdrawal comprising administering to a patient in need of such treatment an effective amount of a D2 receptor agonist.

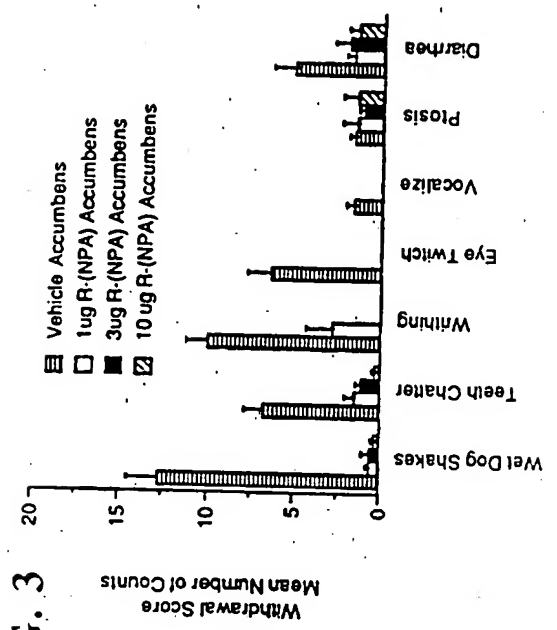


FIG. 1

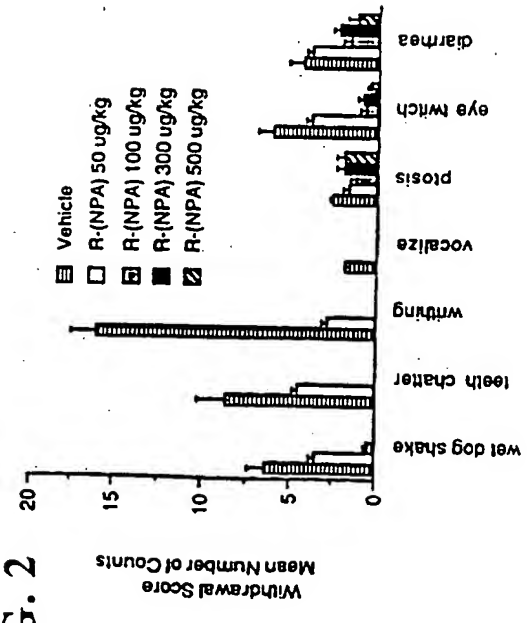


FIG. 2

FIG. 3

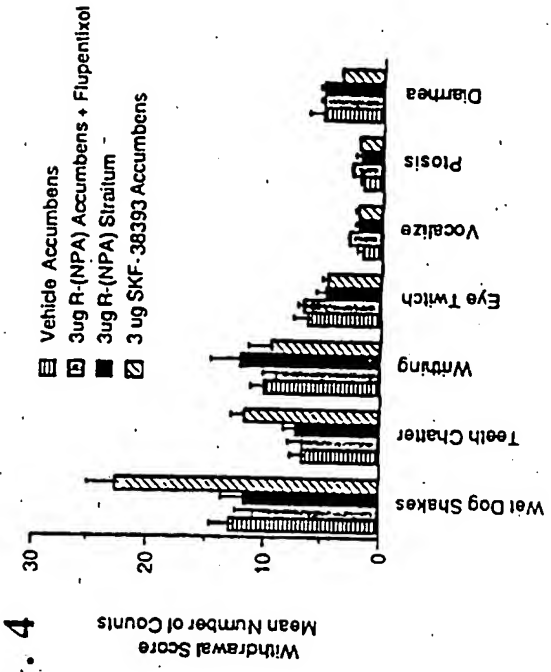
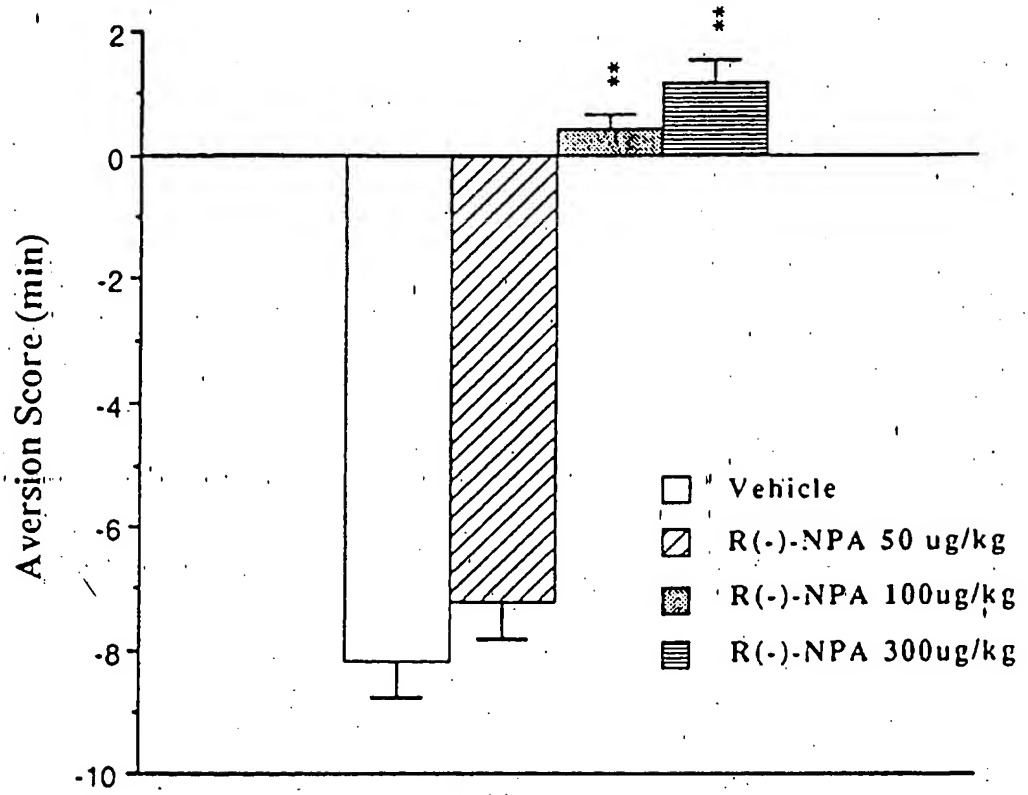


FIG. 4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Vehicle
R(-)-NPA 50 ug/kg
R(-)-NPA 100ug/kg
R(-)-NPA 300ug/kg

FIG. 5

INTERNATIONAL SEARCH REPORT

Int. ..tional application No.
PCT/US94/09116

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/445
US CL :514/284
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/284, 812

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, MEDLINE, EMBASE- SEARCH TERMS: DOPAMINE (D2) RECEPTOR AGONISTS, DOPAMINE AGONIZING COMPOUNDS HEREIN, OPIATE WITHDRAWAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	CHEMICAL ABSTRACTS, VOLUME 98, ISSUED 1982, FERRARI ET AL., "INFLUENCE OF LISURIDE ON MORPHINE WITHDRAWAL SIGNS IN THE RAT: A DOPAMINE-MIMETIC EFFECT", ABSTRACT NO. 46900, PSYCHOPHARMACOLOGY, 78(4), 326-330.	1-5,8 --- 6-7
X --- Y	EMBASE ABSTRACT, ISSUED 1989, GOMAA ET AL., "MODIFICATION OF MORPHINE-INDUCED ANALGESIA, TOLERANCE AND DEPENDENCE BY BROMOCRIPTINE", ABSTRACT NO. 89274686, EUR. J. PHARMACOL., 170(3), 129-135.	1-4 --- 5-8
X --- Y	EMBASE ABSTRACT, ISSUED 1977, BEIL ET AL., " THE USE OF APOMORPHINE IN THE TREATMENT OF ALCOHOLISM AND OTHER ADDICTIONS: RESULTS OF A GENERAL PRACTITIONER", ABSTRACT NO. 78117476, BR. J. ADDICT., 72(2), 129-134.	1,4 --- 2-3, 5-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search 31 OCTOBER 1994	Date of mailing of the international search report 20 DEC 1994
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